ATTACHMENT A
Remarks

Claims 3 and 4 are pending in the present application. By this Amendment, Applicants have amended claim 3. Applicants respectfully submit that the present application is in condition for allowance based on the discussion which follows.

As an initial point, Applicants gratefully appreciate the Examiner conducting a personal interview with their representative, Mr. Stephen Weyer, on August 31, 2006. In accordance with that interview, Applicants have amended claim 3, as discussed during the interview, and further provide the following remarks.

Claims 3 and 4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Nyamekye et al. ("Circulation," 1995, 91:417-425) (hereinafter "Nyamekye") in view of Narciso, Jr. (U.S. Patent No. 5,298,018) (hereinafter "Narciso") and Aizawa et al. (U.S. Patent No. 5,308,861) (hereinafter "Aizawa").

Contrary to the rejection of the claims, the present invention is novel and non-obvious in view of the aforementioned references, individually or in combination with one another. The present method is directed to a unique treatment for preventing restenosis following PTCA treatment. The present method is distinguishable from the prior art methods, such as the method of Narciso, in that the present method is directed to preventing restenosis following angioplasty in a method that: (1) uses substantially less power, i.e. 1 to 10 J/cm^2; (2) irradiates a photosensitive compound at a time point of 0.5-6 hours after the administration of a photosensitizing compound and after an angioplasty treatment has concluded; and (3) has a PDT step which comprises locating a balloon catheter to the position where previous angioplasty has occurred, namely the

angioplasty-dilated and injured site, where the balloon catheter is inflated, which completely intercepts the blood flow at the angioplasty-dilated and injured site.

The present invention is distinguishable and is no way taught or suggested by the prior art. For example, the present invention is in no way obvious from Narciso, which teaches a method for treating arteriosclerosis using a combination of PTCA and repeated steps of administering a photosensitizing compound to block a growth factor binding site of the arteriosclerotic SMC cells injured during a first vascular lumen-widening step. The photosensitizer is re-administered for 5 to 18 days. In a final step, the photosensitizer is irradiated to lyse both the arteriosclerotic plaque and the injured SMC cells. See Narciso, column 4, line 58 to column 5, line 5 and column 2, lines 6-45.

The present invention is distinguishable from Narciso in that Narciso clearly teaches re-administering a photosensitizing compound for 5 to 18 days, followed by irradiation, whereas the present method administers the photosensitizing compound a single time, followed by irradiation within 0.5 to 6 hours after administration. For example, in the present method, NPe6 is administered a single time, either before or after the angioplasty treatment, which is in complete contrast to the Narciso method, which necessarily requires re-administration of the photosensitizer in a growth factor-blocking step (see Narciso, column 2, lines 6-40). Further, Narciso teaches that the re-administering continues for 5 to 18 days where the timing of the administration of the photosensitizer is described as being <u>critical</u> to the Narciso invention (Narciso, column 5, lines 1-4).

A further distinction between the present method and that of Narciso is the location of the inflated balloon catheter during the PDT procedure. In the present

method, the balloon catheter is inflated at the angioplasty-dilated and injured site, i.e. the site of where the previous angioplasty occurred. The inflation of the balloon catheter is such that the bloodstream is occluded and, thus, an outward-exerting force or pressure is applied onto the intravascular wall. Narciso fails to teach or suggest inflating a catheter balloon at the prior angioplasty-dilated site during PDT to exert an outward force or pressure on the blood vessel.

Moreover, it would not have been obvious for one of ordinary skill in the art to inflate a balloon catheter at the site of a previous angioplasty-dilated and injured site, as the art actually teaches away from conducting such treatment at such a site. For example, Honye et al., "Morphological Effects of Coronary Balloon Angioplasty In Vivo Assessed by Intravenous Ultrasound Imaging," pages 1012-1025 of the "Circulation," Vol. 85, No. 3 (March 1992), a copy of which is attached herewith, teaches that the angioplasty-dilated and injured site of an arteriosclerotic arterial blood vessel is subject to dissection, to tearing of the blood vessel wall, and to rupturing of the internal media of the vessel wall, along with other damages. Further, Narciso teaches that subsequently or due to the PTCA or other angioplasty procedure to remove the stenosis of the arteriosclerotic arterial blood vessel, gross damage is done to the intimal surface of the blood vessel, so that such gross damages or injury given to the intimal surface of the blood vessel is accompanied by rupture of the internal elastic lamina, disruption of the arterial wall and atheromatous plaque, as well as separation of the blood vessel tissue layers (see Narciso, column 3, lines 50-60; column 4, lines 4-8; and column 8, lines 7-13). Therefore, one of ordinary skill in the art would know that the angioplasty-dilated and injured site of an arteriosclerotic arterial blood vessel is <u>very weak</u> in its

mechanical strength and, hence, subsequently applying a balloon catheter to the angioplasty-dilated and injured site is contraindicated and should be avoided to prevent subjecting the blood vessel to an outward-exerting force or pressure which could possibly lead to the blood vessel inadvertently bursting at the injured site or possibly invoking a lethal risk of potential injury to the patient. Therefore, it would not have been obvious for one of ordinary skill in the art to conduct a PDT procedure by inflating a balloon catheter at the angioplasty-dilated and injured site following an angioplasty treatment.

Furthermore, Narciso fails to teach or suggest employing a balloon catheter to completely inflate at an angioplasty-dilated and injured site following angioplasty treatment during a PDT step. Although Narciso (column 6, lines 61-66) states "If the photosensitizer used is HPD, total occlusion of the blood may be necessary to minimize attenuation of the therapeutic light by the blood," this sentence does not imply or suggest that one of ordinary skill in the art should use a completely inflated balloon during the PDT step so as to put the balloon catheter in tight contact with the vascular inner wall of the angioplasty-dilated and injured site after the angioplasty step in order to effect a complete interception of the bloodstream at the angioplasty-dilated and injured site, as claimed. As previously noted, doing so would be contraindicated and, moreover, against the clear teaching in the art, which teaches away from inflating a balloon catheter at the angioplasty-dilated and injured site due to the possible gross damage which may occur at the angioplasty-dilated and injured site.

Yet, a further distinction of the present method from that of Narciso is that the present method is directed specifically to the prevention of restenosis, whereas Narciso

is directed to blocking the growth factor of SMC cells and treating arteriosclerotic lesions and plaques themselves using a PDT procedure which lyses the lesions or plaques and the injured SMC cells.

A further distinction of the present invention over the prior art, including Narciso, is the use of a low laser fluence, as compared to that of Narciso, and which is conducted in a single irradiating step after a single administration of a photosensitizing material, which results in successful prevention or inhibition of restenosis (see present specification, page 8, lines 17-23; page 14, lines 22-25; page 15, lines 2-8; page 17, lines 4-17). An advantage of the present method is the use of a lower laser fluence which inhibits restenosis and provides no or few side effects which could result from a higher laser irradiation energy.

Evidence of the advantage of the present invention is provided in Examples 1 and 2 of the present specification and, in particular, by the results shown in Table 1 of Example 2 at page 39. The restenosis inhibition rate obtained with the method of the present invention and, in particular, even with a laser fluence of 50 J/cm^2 is not only as efficient as the inhibition rate observed with the comparative treatment of Table 1 performed with a 2-folds higher laser fluence of 100 J/cm^2 and with the cylindrical optical fiber device, but the restenosis inhibition rate obtainable by the present invention is actually <u>1.5 times higher</u>.

Additionally, reference is made to the data and evidence of the previously submitted Rule 132 Declaration of Dr. Nagae (hereinafter "Nagae Dec.") submitted with the Amendment of February 13, 2006, which supports the advantageous and surprising effects of the method in accordance with the present invention.

As discussed at pages 5-7 of the Nagae Dec., the present inventors have conducted supplemental experiments using the protocol as described in Example 2 of the present application, except that NPe6 was used at doses of 2.5 and 5 mg/kg, and the laser fluence for the intravascular laser irradiation was set at 1 and 10 J/cm^2. At the end of two weeks after the PDT procedure, the cross-sectional area of the lumen of blood vessels at the angioplasty-injured site as treated or not treated with PDT was measured. As shown in Table A, at page 6 of the Nagae Dec., the lumen at the PDT-treated site was increased by about 2.5 times when subjected to the method in accordance with the present invention, and the inhibition of new-intima thickening is reduced by at least 7 times.

Therefore, the present method provides the unexpected, striking and surprising advantage of obtaining a higher rate of restenosis inhibition with a lower level of laser fluence than that expected with a previously known method of the Japanese language article of Dr. Nagae et al. described in the Japanese document of "62nd Scientific Meeting of Japanese Circulation Society, Abstract, p. 465 (1998) (hereinafter "Dr. Nagae et al.") cited at page 8, lines 8-9 of the present specification, wherein a cylindrical optical fiber device was employed for the intravascular laser irradiation in the PDT procedure of inhibiting the vascular lumen restenosis inducible after the interventional angioplasty and the PDT procedure was effected at a laser fluence of 100 J/cm^2 (see the comparative test in Table 1 at page 39 of the present application).

Enclosed herewith is a copy of the above-mentioned Japanese document along with an English translation of the relevant Japanese language article of Dr. Nagae et al., as described at page 465, right column, item No. P319 of this Japanese document.

In Example 2 of the present application, it is simply stated that the balloon is inflated within the artery to intercept the bloodstream within the blood vessel. In fact, however, it is nearly impossible in actual animal experiments (based on the Applicants' experiments) to completely occlude the blood flow using an inflated balloon catheter without outwardly expanding the blood vessel due to the outward force exerted by the inflated balloon (Nagae Dec., ¶ 11). The latter experimental fact of the arterial vessel being distended by the completely inflated balloon has always been observed by the present inventors during the procedures of Examples 1 and 2 of the present application.

In more detail, in Example 2, as described at page 37, lines 17-27 of the present application, the complete inflation of the balloon of the balloon catheter was conducted to such an extent as to completely intercept the bloodstream at the angioplasty-dilated site (see Figure 2 of the present application). Upon complete balloon inflation, although not described in the present application, the blood vessel, at the angioplasty-dilated site, was distended outward by the completely inflated balloon, and also the cross-sectional area of the vascular lumen at the angioplasty-injured site of the blood vessel was actually increased significantly due to the inflated balloon, as compared with the original cross-sectional area of the vascular lumen which could be observed before the complete inflation of the balloon. However, based on the disclosure, it is inherent that the blood vessel would be extended upon balloon inflation (see, e.g., Nagae Dec., ¶ 11).

Thereafter, the PDT procedures with the intravascular irradiation of laser light was done as described at page 37, lines 3-7 as well as at page 37, the last line to page 38, line 9 of the present application. At the end of two weeks after the PDT

procedure, it could be observed, in fact, that the PDT-treated site of the blood vessel having received the PDT procedure with the completely inflated balloon of the intravascular balloon catheter and with the intravascular laser irradiation via the completely inflated balloon, in accordance with the presently claimed method, continues to have the cross-sectional area of the vascular lumen, which was once increased significantly larger than the aforesaid original cross-sectional area of the vascular lumen which was observed before the complete inflation of the balloon of the intravascularly inserted balloon catheter. If necessary, these results can be provided in a subsequent or Supplemental Rule 132 Declaration.

An additional advantage of the present invention is the effect of increasing the cross-sectional area of the vascular lumen. Such meritable effect is one of the remarkably advantageous and unexpectable effects of the present method, that is entirely unpredictable and unexpectable from the cited prior art references. The Nagae Dec. reveals that the above-mentioned meritable effect of increasing the cross-sectional area of the vascular lumen can be obtained according to the present method.

Furthermore, notwithstanding the Examiner's assertion in Section 4 of the outstanding Office Action, Narciso does not teach or suggest a photodynamic therapy during the PTCA procedure to limit restenosis of a blood vessel anywhere in its disclosure, let alone in the abstract. To the contrary, Narciso clearly discloses that a light-irradiating PDT step is conducted after a growth factor-blocking step which is effected after a lumen-widening step, namely a PTCA or PTA procedure. Therefore, Narciso fails to teach or suggest a photodynamic therapy <u>during</u> PTCA procedure.

Further, contrary to the Examiner's statement, "Narciso specifically explains that the use of a photodynamic agent can be during, before or after a PTCA procedure," Narciso does not teach using a photodynamic agent, as alleged. In fact, Narciso, column 2, lines 6-65 discloses not only a first administration of a photosensitive agent, which may be done during, before or after the lumen-widening step, such as PTCA, but also that repeated, re-administration of the photosensitive agent is required during the growth factor-blocking step subsequent to the lumen-widening step. Thus, Narciso clearly teaches that the photodynamic agent must be administered repeatedly, after the PTCA procedure.

A further distinction of the present method from that of the Narciso method is that the photosensitizer in Narciso is a competitor which inhibits the growth factor capable of binding to the growth factor-binding site of injured SMC cells and also acts as an agent that can involve the lyses of both the arteriosclerotic plaque and the injured SMC cells during the subsequent PDT step with the light irradiation.

An additional distinction of the present method from that of Narciso is the use of NPe6 as a photosensitizer in the present treatment. In the Office Action, the Examiner said that Narciso suggests that NPe6 can be used as an effective photosensitizer active at a light wavelength of 660 nm wavelength, citing Narciso, column 7, table 1, under class Phorobides. However, absent impermissive hindsight, one of ordinary skill in the art would not be motivated to use NPe6 based on Narciso for the PDT method for a treatment of the angioplasty-dilated and injured site of the vascular vessel for the purpose of inhibiting possible restenosis, as claimed, because it is evident that the Narciso methods are exclusively directed to the treatment of the atherosclerosis which

is explicitly distinguishable and distinct from the present PDT treatment of the angioplasty-dilated and injured site of the vascular vessel for the restenosis-inhibiting purpose, as claimed.

Moreover, the Examiner is inaccurate in saying "Since Narciso teaches the use of photodynamic therapy during a PCTA procedure, all method steps of the instant claims are also inherently disclosed." As will now be clear from the remarks made herein, Narciso does not teach the use of the PDT procedure <u>during</u> the PCTA procedure and, hence, it is evident that all method steps of the present claims are <u>not</u> inherently disclosed by Narciso, contrary to the Examiner's allegation in this matter.

In addition, the present invention is distinguishable from the other cited references of Nyamekye, Aizawa and Jenkins.

For example, the present method is distinguishable from Nyamekye in that the present method uses a significantly lower laser fluence, namely 1 to 10 J/cm^2, as compared with 50 J/cm^2, and the present method uses mono-L-aspartyl chlorin e6, whereas Nyamekye uses 5-ALA, a chemically unrelated compound.

Furthermore, the present method recites a laser fluence which is in no way obvious from Narciso, individually or in combination with Aizawa. The present method is directed to a completely different PDT treatment at the angioplasty-dilated and injured site of a vascular vessel to prevent restenosis, which is a completely different condition from that of the prior art, in that the present method is directed at inhibiting possible restenosis inducible after an angioplasty treatment, whereas the prior art is directed at a completely different treatment, namely lysing plaques or lesions and SMC cells. Therefore, it would not have been obvious to one of ordinary skill in the art to modify the

higher laser fluence taught in the prior art to use the lower fluence of 1 to 10 J/cm^2. Furthermore, it would take more than routine experimentation and certainly would be unpredictable from the teachings of Narciso and Aizawa to use the claimed laser fluence power.

In conclusion, Nyamekye, Aizawa and Narciso fail to teach that the restenosis of the blood vessel, which is inducible after the angioplasty procedure, can be efficiently and successfully inhibited with a single administration of NPe6 at a significantly reduced dosage of 0.1 to 5 mg/kg, immediately after an angioplasty procedure and by effecting the intravascular irradiation of laser light of 664 nm at a significantly reduced laser fluence of 1 to 10 J/cm^2 by means of the completed inflated balloon of the intravascularly inserted balloon catheter with the co-current complete interception of the bloodstream flowing between the completely inflated balloon of the catheter and the inner wall side of the blood vessel at the angioplasty-dilated and injured site, as claimed.

The novel combination of the features or elements, as recited in claim 3, is unpredictable from Nyamekye, Aizawa and Narciso, either alone or in combination. That the efficient inhibition of a restenosis of the blood vessel inducible after the angioplasty can be achieved with success, as claimed, is entirely unexpectable by one of ordinary skill in the art from the teachings of Nyamekye, Aizawa and Narciso.

Finally, in the Office Action, claims 3 and 4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Jenkins, in view of Narciso and Aizawa. The newly cited reference of Jenkins, entitled "British Journal of Surgery," Vol. 86, No. 10, pages 1258-1263 (1999) was published in October 1999 and, therefore,

published after the claimed priority date of 2 April 1999, entitled by Japanese Patent Application No. 11-95654. Therefore, Jenkins is not prior art citable against the present application. If necessary, Applicants will submit a certified English translation of the Priority Document (Application No. 11-95654) establishing that Jenkins is not prior art of the present application.

Moreover, Jenkins (page 1259, right column, lines 5-14) discloses that a 200 micro-meter laser fiber with a 4-cm diffuser is employed for the PDT procedure using ALA as the photosensitizer and a light of 635 nm at a laser fluence of 50 J/cm^2. Thus, it is clear that all the Examiner's allegations set forth in Sections 9, 10, 11 and 12 at page 6 of the Official Action are not well grounded.

Based on the foregoing, Applicants respectfully submit that the present invention, as provided in claims 3 and 4, is not obvious in view of the prior art.

In view of the foregoing, Applicants respectfully submit that the present application is in condition for allowance.

END REMARKS

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ABSTRACTS

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P318

血管再狭窄予防法としての血管内照射療法の開発と作用機序の解明

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【目的】新しい再狭窄予防法として血管内照射療法(IVRT)が開発された。IVRTは血管内に線源を短期間留置する方法と、放射活性ステントを植え込む方法が考案されている。我々は、高線量ガンマ線源を短時間血管内に留置する方法と、ベータ線を発生するステントを植え込む方法を開発した。本研究は、IVRTの効果の確認とその平滑筋増殖抑制機序の解明を目的とした。【方法】[IVRTの開発]家兎の総頸動脈をバルーンで拡張後にガンマ線源として192Ir針を付けたカテーテルを短時間(30-120分間)留置し照射を行った。また、ベータ線源として133Xeをイオンインプランテーション法により表面を放射活性化したステントを作成、家兎腹部大動脈に植え込んだ。照射2週目に血管を摘出し、形態学的に観察した。対照群には放射活性のない Ir 針あるいはステントを用いた。[IVRTの効果の確認と機序の解明]新生内膜の面積から効果を検討し、新生内膜の細胞形質の変化はHE染色と転写因子(BTEB2とSP1)の免疫染色により解析した。【結果】1：IVRTにより新生内膜の形成は抑制された。2：転写因子BTEB2とSP1は192Ir照射群の新生内膜で対照群に比較して発現が著明に抑制された。【考案】IVRTは新生内膜の転写因子の発現を抑制し、新生内膜増殖予防に効果を示すと考えられる。

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Mono-L-aspartyl chlorin e6による血管内膜肥厚に対するPhotodynamic therapy：新しく作成したCylindrical fiberによる血管内腔全周照射の実験的検討

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(目的) Photodynamic Therapy (PDT)の新生内膜肥厚 (IH) 抑制の有用性が報告されている．我々は従来のHPDより組織の自家蛍光の影響が少なく，励起効率が高い，新しい光感受性物質Mono-L-aspartyl-chlorin e6 (NPe6)を使用し，IH治療応用を検討している．今回，作成したCylindrical diffusing fiberにより，血流非遮断下に血管内よりPDTを行い，IH抑制効果につき検討した．(方法) Cylindrical fiberは 径0.5 mm，発光部15 mm である．Npe6励起にはPDT用半導体レーザー(664 nm)を使用した．蛍光はNoch filterにて励起光をカットしCCDカメラで観測した．fiber特性：100mW入力時，照射面から2.5mmで20mW/cm2．実験(I) albumin ＋ 2つのNPe6溶液濃度 35ug/ml,14 ug/mlとゼラチンを混合し，10mW/cm2照射で蛍光発生範囲を比較した．実験(II)NZW rabbitに，NPe6 (2.5mg/kg)を投与後 balloon cathe.による腹部大動脈傷害モデルを作成．投与3時間後，傷害部動脈に内側照射し(100 J/cm2)，4日後，2週間後の病理学的検討を行った．(結果) fiberは側方に全周照射された．蛍光範囲は低濃度が高濃度に比べ広く，NPe6の励起光吸収によると考えられた．血中低濃度相当の投与後3時間にPDTを行った．PDT中，励起光カットでNpe6の蛍光を外側から確認しえた．PDT4日後の病理では血管内外側の広範囲にaccelular arterial wallが観察された．14日後には周囲より細胞浸潤を認めたが，中膜内側にaccelular layerが見られ，IH抑制効果が観察された．(結語) IH抑制方法としてIntervention時，cylyndrical fiberによる局所NPe6-PDT併用の有用性が示唆された．

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TFPIは血栓抑制と新生内膜抑制の異なる効果により再狭窄を予防しうる。

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【目的】TFPI(Tissue Factor Pathway Inhibitor)はXa因子依存性にVII因子の活性を阻害するプロテアーゼインヒビターである。抗凝固作用のほか培養平滑筋細胞の増殖抑制作用が明らかにされてきた。TFPIの局所投与による再狭窄予防効果判定を実験動物で行った。【方法】日本白色家兎(2.5-2.9Kg)の腸骨動脈にIVT社製Cutting Balloon 2.5mmを用いPTAを行なった。PTA直後にE-Z EM社製Pulse Spray (drug delivery system)をPTA施行部位に留置し、TFPIを 40μg／ml／回を1分毎に5回(計200μg)局所投与した(TFPI群)。対照は1%アルブミン1ml／回を1分毎に 5回投与した(コントロール群)。TFPIの急性期効果と慢性期効果を検討した。i)TFPIの急性期効果は術直後、術2日後にみられる内弾性板切断部位のフィブリン血栓の有無、ii)TFPIの慢性期効果は術4週後の新生内膜／中膜面積比である。【結果】i)急性期効果；術2日後のフィブリン血栓形成率はTFPI群10%、コントロール群51%であった(P＜0.0001)。ii)慢性期効果；術4週後の新生内膜／中膜面積比はTFPI群が0.118±0.130、コントロール群が0.342±0.219であった(P＝0.030)。【総括】TFPIは急性期効果としてフィブリン血栓形成を抑制し、慢性期効果として新生内膜形成を抑制する。これら異なる2つの機序によりPTCA後再狭窄予防効果が期待できる。

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Cilostazolはstent植え込み後の再狭窄に対して有効か？ -ブタ冠動脈を用いた再狭窄モデルにおける検討-

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【目的】抗血小板剤であるCilostazolのstent後再狭窄病変に対する臨床効果がいくつか報告されているが、基礎的な検討はほとんどない。そこでブタ冠動脈を用いてstent植え込み後の再狭窄モデルを作製し、Cilostazolの抑制効果を検討する。【方法】ブタのLADにPTCA用balloon(3.0mm径)で拡張を行い、その14日後に血管造影で狭窄性変化を確認後、同部位にPalmatz-Schatz stent(3.0mm径)を植え込んだ。Control群(C群、n=8)には通常の餌を、Cilostazol群(Ci群、n=8)には通常の餌にCilostazolを30mg/kg/dayを混ぜてstent植え込み3日前より一日2回経口投与した。両群ともに植え込み後28日で解剖し以下の組織学的検討を行った。組織収縮性の少ない樹脂に包埋後、最小血管径部位でstentを含めて薄切しH.EおよびE.V.G染色を行い、各々Lumen(L)、Intima(I)、Media(M)、Adventitia(A)、%Stenosis(S)=100×(Intima/Intima+Lumen)を計測し、両群で統計学的検討を行った。(面積の単位はmm^2)【結果】C群では(L)2.4±0.7 (I)4.1±1.2 (M)1.0±0.3 (A)2.1±0.4 (S)62.2±11.6であったのに対してCi群では(L)3.6±1.2 (I)2.8±0.9 (M)1.2±0.2 (A)1.8±0.5 (S)43±12であった(Mean±S.D.)。統計学的にCi群はC群と比較してLumenで有意に大で、%Stenosisにおいて有意に小であった(P＜0.05)。尚、Cilostazolの血中濃度はstent植え込み時には1.95μg/mlで、解剖時には1.57μg/mlであり、臨床における濃度に近似していた。【総括】ブタ冠動脈において臨床使用量とほぼ同程度の血中濃度で有意な抑制効果が認められたことより、stent植え込み後の再狭窄病変に対してCilostazolが有効である可能性が示唆された。

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Photodynamic therapy with mono-L-aspartyl chlorin e6 against thickening of a vascular intima of blood vessel: Experimental investigations of laser light irradiation on the whole face of a vascular lumen of blood vessel

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(PURPOSE) Some reports are made on utilities of photodynamic therapy (PDT) for suppression of a thickening of a vascular intima, namely intimal hyperplasia (IH). Previously, we have made investigations of therapeutic treatment of IH with application of a new photosensitive substance, mono-L-aspartyl-chlorin e6 (NPe6) which can little be affected by a self-fluorescence of a tissue but has a higher efficiency of photo-activation of the photosensitizer than the previously known HPD. Now, we have conducted an intraluminal PDT by means of a cylindrical diffusing fiber as newly manufactured, without intercepting the flowing of bloodstream, whereby the effects of such PDT on the suppression of IH are examined.

(PROCEDURE) The cylindrical fiber used had a diameter of 0.5 mm and a light-emitting part of 15 mm in length. For the photo-activation of NPe6, there was employed a laser light (664 nm) which was produced by a semi-conductor for PDT. The fluorescence of NPe6 was observed by a CCD camera with cutting the photo-activating light by a Notch filter. Characteristics of the cylindrical fiber were such that the intensity was 20 mW/cm^2 at a distance of 2.5 mm from the irradiated face when a power input was set at 100 mW.

EXPERIMENT (I): albumin and one of two solutions of NPe6, namely a solution containing NPe6 at its concentration of 35

μg/ml or a solution containing NPe6 at its concentration of 14 μg/ml, as well as gelatin were mixed together to prepare two mixtures to be tested. These two mixtures under test were compared with each other in respect of the range of emission of their fluorescence under light irradiation at 10 mW/cm^2.

EXPERIMENT (II): NPe6 was administered at a dose of 2.5 mg/kg to NZW rabbits, which were then treated to prepare the rabbit model having an injury site in the abdominal aorta by means of a balloon catheter. At a time of 3 hours after the administration of NPe6, the intraluminal irradiation of the laser light was made at 100 J/cm^2 on the artery at the injured site. 4 Days and two weeks later, the pathological assessments were conducted.

(RESULTS) The cylindrical fiber emitted the laser light laterally to irradiate the whole face of the inner wall of the artery blood vessel. It was observed that the range of the fluorescence produced was wider at the lower concentration of NPe6 than the higher concentration of NPe6, probably owing to that NPe6 at the higher concentration could absorb much highly the photo-activating light. PDT was carried out at a time of 3 hours after the NPe6 administration, when the concentration of NPe6 in the plasma was reduced to the lower concentration mentioned in said Experiment I. The fluorescence could be observed during PDT from the outside of the blood vessel with cutting the photo-activating light by a Notch filter. When pathological assessment was made at the end of 4 days after PDT, it was observed that accelular arterial wall was formed in broad regions at the inner side of the vascular vessel. 14 Days later, the cellular infiltration was observed. While, the accelular layer was found at the inner side of the tunica media, revealing that the effects of suppressing IH were attained.

(CONCLUSION) The combined application of NPe6 and PDT at the lesion site with use of the cylindrical fiber is useful for a

method of suppressing IH when an intervention is conducted.